Arterial Baroreflex Impairment in Patients During Acute Coronary Occlusion

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Objectives. **We tested whether acute coronary occlusion interferes with arterial baroreceptor control of heart rate in humans.**

Background. **Subnormal baroreflex sensitivity (BRS) is an important risk indicator for sudden death. Animal research indicates that both chronic myocardial infarction and acute coronary occlusion impair baroreflex modulation of heart rate.**

Methods. **We measured RR interval prolongation after phenylephrine-induced systolic pressure increases before and during 2-min coronary occlusions in 47 patients (27 men) undergoing clinically indicated single-vessel coronary angioplasty for stenoses in the proximal or midportion of the vessel causing >50% reduction in the arterial diameter, with normal antegrade flow (33 anterior descending, 10 circumflex, 4 right coronary artery). A control group of 11 patients treated for chronic total occlusion of a coronary artery was assessed to evaluate nonspecific changes in baroreflex function during a 2-min balloon inflation in the occluded artery.**

Results. **The BRS decreased from 5.2 ± 3.8 (mean ± SD) to 4.1 ± 3.5 ms·mm Hg^{-1} ($p = 0.01$) during the coronary occlusion in the 28 patients with preserved arterial baroreceptor control of heart rate—that is, adequate blood pressure responses and correlation coefficients of the slopes both in baseline and during coronary occlusion. The same phenylephrine dose increased systolic pressure less during than before coronary artery occlusion (21 ± 21 versus 36 ± 16 mm Hg, $p < 0.0001$), and in 6 patients it failed to prevent systolic pressure reduction during occlusion. Correlation coefficients of the baroreflex regressions decreased from 0.81 ± 0.27 to 0.47 ± 0.44 ($p < 0.0001$) during coronary artery occlusion in the 41 patients with adequate systolic pressure rises in both phenylephrine tests, and the association between RR intervals and rising systolic pressures was lost in 13 patients during coronary occlusion. Balloon inflation in a chronic total occlusion of a coronary artery did not cause significant changes in BRS (from 5.3 ± 4.0 to 5.2 ± 3.7 ms·mm Hg^{-1}), correlation coefficient of the slope or phenylephrine-induced pressure rise.**

Conclusions. **Our study shows that abrupt coronary occlusion impairs baroreflex modulation of vagal and sympathetic nervous outflow in humans.**

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Animal studies suggest that arterial baroreflex control of heart rate and vascular resistance is impaired during acute myocardial ischemia (1–5). Impairment of the baroreceptor-heart rate control has also been observed in humans after myocardial infarction and during episodes of myocardial ischemia (6–9). Acute coronary occlusion may cause a wide range of autonomic reactions as evidenced by changes in heart rate, blood pressure and heart rate variability (10–12), but there are limited data on potential changes of human arterial baroreflex function during acute coronary occlusion. Because abrupt occlusion of a coronary artery is a major cause of sudden cardiac death (13) and experimental studies suggest that low baroreflex sensitivity (BRS) is a marker of increased risk of ventricular fibrillation during acute coronary occlusion (14–16), we assessed the effects of acute coronary occlusion on baroreflex control of the circulation in a prospective series of patients undergoing clinically indicated coronary angioplasty.

Methods

Study population. The study population comprised 47 consecutive patients (27 men) fulfilling the following criteria: 1) single-vessel coronary angioplasty; 2) stenosis in the proximal or midportion of the vessel causing >50% reduction in the arterial diameter with normal antegrade flow (Thrombolysis in Myocardial Infarction [TIMI] grade 3 flow) (17); 3) documented myocardial ischemia; 4) no history of acute myocardial infarction and no or minimal wall motion abnormality in the myocardial territory at risk; 5) sinus rhythm and no bundle

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Abbreviations and Acronyms
BRS = baroreflex sensitivity
TIMI = thrombolysis myocardial infarction

branch block; 6) tolerance to >60-s coronary occlusion; 7) no acute procedural complications; and 8) informed consent of the patient. The clinical characteristics of the study population are described in Table 1.

A control group of 11 patients (6 men, mean age 55 years) treated for a chronic total occlusion (TIMI grade 0 or 1 flow) of a coronary artery (5 left anterior descending, 1 left circumflex and 5 right coronary artery) was assessed to evaluate potential nonspecific changes in baroreflex function during a 2-min balloon inflation in the occluded artery.

Study protocol. The design was approved by the Ethical Committee of the institution and all patients gave their informed consent. Coronary angioplasty was performed by a usual technique (18). Diazepam 5–10 mg was given as premedication. Sublingual nitroglycerin was given before the guiding catheter was placed in the coronary ostium and every 15 min thereafter. None of the patients were given atropine. In cases of tight coronary artery stenosis, the deflated balloon, or even the guide wire, may compromise blood flow in the vessel, so that observations made before and during the first balloon inflation may be inconsistent and unreliable. Thus, an initial short balloon angioplasty (≤20 s) was performed as soon as possible after introduction of the balloon into the stenosis. Normal coronary flow was ascertained with a contrast medium injection after this predilatation.

Two successive balloon inflations with similar inflation pressures (4–8 bars) and duration were performed at 5-min intervals. These inflations, which were used for data acquisition, were designed to last up to 120 s, unless intolerable chest pain, hemodynamic instability or ventricular ectopy necessitated earlier deflation of the balloon (19). The purpose of the first balloon inflation was to evaluate ischemia-induced hemodynamic reactions (12,18) and to ensure tolerance of each patient for at least 60 s of coronary occlusion. Based on the information derived from the first occlusion, a phenylephrine bolus was given during the second balloon inflation, about 60 s before the estimated end of the occlusion. No contrast medium was injected during data acquisition, and every effort was made to keep the patients unaware of the timing of the balloon inflations and to maintain the circumstances as stable as possible so as to minimize the effects of nonspecific distress on heart rate or blood pressure.

Patients were accustomed to breathing at a constant rate of ~0.25 Hz from the beginning of the catheterization and were advised to avoid unnecessary talking, especially just before or during data acquisition. In cases of intolerable chest pain during this phase of the procedure the patients were advised to give a hand signal and the balloon was deflated. The intensity of chest pain during balloon inflation was assessed on Borg's numerical scale (1–10) immediately after balloon deflation (20). The precordial lead that provided the largest R wave deflection was chosen for on-line electrocardiogram (ECG) monitoring.

Coronary anatomy. Coronary angiography in at least four projections with cranial and caudal angulated views was performed before the angioplasty; the view with the best visualization of the lesion was selected and the severity of the coronary artery stenosis was measured using the stenosis diameter program included in the Philips DCI S System. The presence of collateral flow was graded according to Cohen and Rentrop (21).

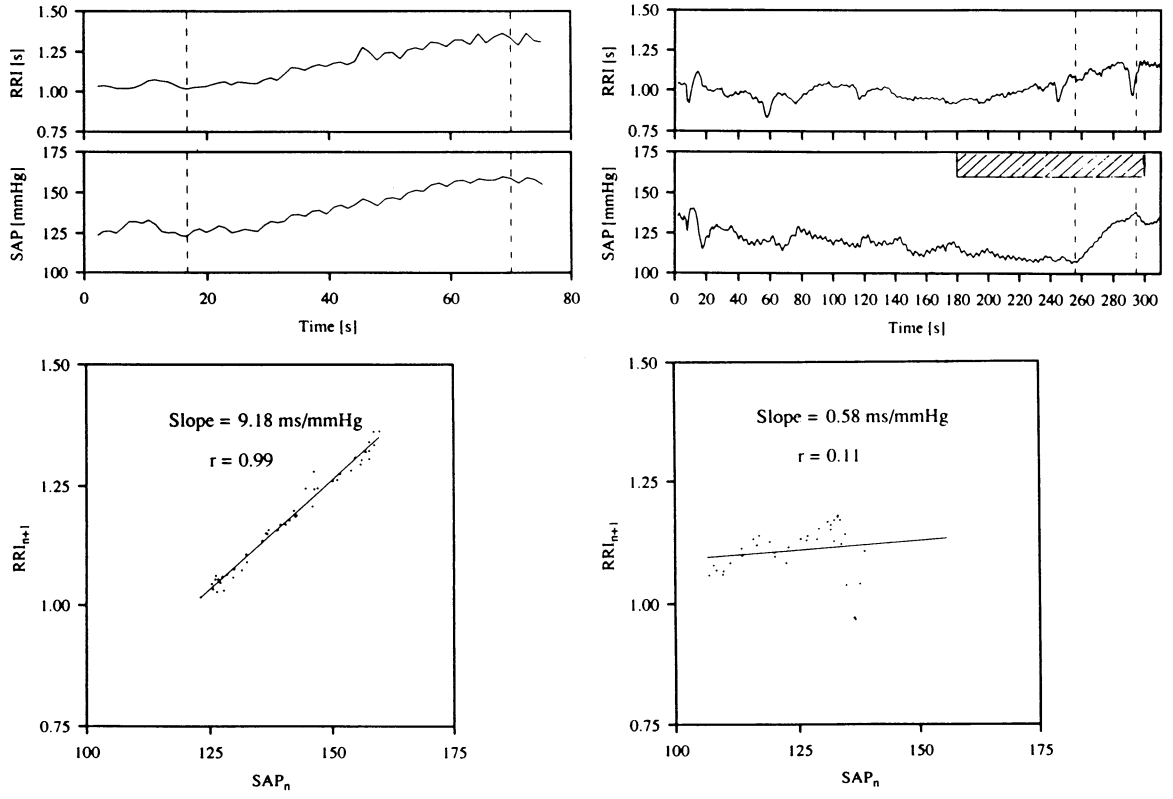
Heart rate and blood pressure data acquisition and analysis. Continuous ECG and blood pressure recordings were made during phenylephrine testing and immediately before and during the first 2-min balloon inflation (Fig. 1). All data acquisition and analyses were performed by a method previously described in detail using a menu-driven software package (CAFTS, Medikro Oy, Kuopio, Finland) (11,18). The RR intervals were collected from the surface ECG and arterial pressure was measured from the femoral artery using external transducers. Stationary regions, excluding ectopic beats, were selected for the analysis of heart rate, heart rate variability and blood pressure. The baseline data were analyzed from a region of approximately 60 s just before the first 2-min occlusion, and a similar region at the end of the first 2-min balloon occlusion was selected for occlusion data. The root-mean-square of the differences between successive RR intervals was calculated using standard equations. Heart rate and blood pressure reactions during the first coronary occlusion were classified according to an earlier control group (18).

Phenylephrine testing. The baseline phenylephrine test was done after coronary angiography, 5 to 10 min before the

Table 1. Clinical Data, Cardiovascular Medications at the Time of the Angioplasty and Angiographic Characteristics of the Study Group (47 Patients)

Age (years)	57 ± 10
Hypertension	11 (23%)
History of chest pain (months)	14 ± 21
Diabetes	4 (9%)
Beta-blocker	25 (53%)
Calcium antagonist	6 (13%)
Long-acting nitrate	33 (70%)
Stenosis severity (%)	84 ± 8
Occluded artery	
Left anterior descending	33 (70%)
Left circumflex	10 (21%)
Right coronary	4 (9%)
Visible collaterals	5 (10%)
Heart rate (beats/min)	69 ± 13
Systolic blood pressure (mm Hg)	146 ± 30
Diastolic blood pressure (mm Hg)	81 ± 12
Occlusion time(s)	114 ± 14
Chest pain	41 (87%)
ST changes	28 (60%)

Data presented are mean value ± SD or number (%) of patients.



first coronary occlusion. A 150-μg bolus of phenylephrine was injected intravenously via a peripheral vein. The baseline test was repeated in two cases with a phenylephrine bolus of 200 μg to achieve a rise in systolic pressure ≥15 mm Hg. The phenylephrine test was repeated during the second coronary occlusion. The last phenylephrine dose used in the baseline study was given after 30 to 60 s of coronary occlusion. The slope of the linear relationship between the length of RR interval (in ms) and the preceding systolic pressure value (in mm Hg) from the analysis window (that is, from the beat which started the sustained rise in systolic pressure to the beat after the maximal pressure elevation) was calculated by the CAFTS software using linear least-mean-squares fitting to obtain baroreflex slope (22) (Fig. 1). Only the slopes with statistically significant ($p < 0.05$) positive associations between RR intervals and preceding systolic pressures were accepted.

Statistical analysis. All analyses were performed using the SPSS for Windows, Release 6.0, and data are presented as mean ± SD. Nonparametric Wilcoxon test was used for intragroup comparisons. Categorical variables were compared using the chi-square test and Fisher's exact test. The Mann–Whitney test was used for the comparison of continuous variables. Linear regression analysis was used to assess predictors of BRS, and stepwise logistic regression analysis was employed to assess the independent predictors of loss of integrity of arterial baroreflex during coronary occlusion.

Figure 1. Computer output of beat-to-beat RR intervals and invasive systolic blood pressure (SAP) during phenylephrine tests in the baseline (**left upper panel**) and during balloon occlusion (**right upper panel**) of a 90% stenosis in left anterior descending coronary artery in a 58-year-old male patient. The lower panels show respective baroreflex slopes derived from the time windows shown by broken vertical lines in the upper panels. In this case, coronary occlusion (**hatched bars, right upper panel**) causes a mild, progressive bradycardia already before the phenylephrine bolus. Phenylephrine bolus (150 μg) causes a rise in systolic blood pressure, but at the end of the coronary occlusion RR intervals suddenly shorten despite continuing pressure rise. Baroreflex sensitivity could not be calculated because of the loss of linear relationship between the RR intervals and the preceding systolic blood pressure values despite adequate blood pressure reaction during coronary occlusion in 13 patients.

Results

Heart rate, blood pressure and heart rate variability. There were no significant changes in the mean values of systolic blood pressure, heart rate and the root-mean-square of the differences between successive RR intervals during the first 2-min coronary occlusion, but diastolic blood pressure and standard deviation of RR intervals increased during the occlusion ($p < 0.05$ for both). When the individual responses were compared to an earlier control group (18), a marked bradycardic reaction (≥8 beats/min) occurred in six women and was accompanied by a hypotensive reaction—that is, >17 mm Hg drop in mean systolic blood pressure—in three cases. Hypotensive reactions occurred in two additional patients (1 wom-

Table 2. Comparison of Phenylephrine Tests in the Baseline and During Coronary Occlusion

	Baseline	Occlusion	p Value
RR interval before phenylephrine (ms)	879 ± 147	895 ± 139	NS
Systolic blood pressure before phenylephrine (mm Hg)	136 ± 26	145 ± 30	<0.05
Rise in systolic blood pressure after phenylephrine	36 ± 16	21 ± 21	<0.0001
Correlation coefficient of slope*	0.81 ± 0.27	0.47 ± 0.44	<0.0001
Baroreflex sensitivity (ms·mm Hg^{-1})†	5.2 ± 3.8	4.1 ± 3.5	0.01

Values are mean ± SD. * = Data on 41 patients with adequate blood pressure rise after both phenylephrine injections; † = data on 28 patients with adequate pressure rise and correlation coefficient of the baroreflex slope after both phenylephrine injections.

an). A tachycardic reaction (≥8 beats/min) was observed in one man and one woman and was accompanied by a hypertensive reaction (>23 mm Hg) in the woman. Two other patients (1 woman) had a hypertensive reaction without significant heart rate change.

Phenylephrine testing. The same phenylephrine dose increased systolic pressure less during than before coronary artery occlusion (21 ± 21 vs. 36 ± 16 mm Hg, $p < 0.0001$) (Table 2). In six patients, phenylephrine failed to prevent the coronary occlusion-induced reduction in systolic pressure. In four of these patients, the fall in systolic blood pressure was associated with paradoxical bradycardia (Fig. 2), and in two cases no significant heart changes were observed. Because of the loss of arterial baroreceptor-mediated heart rate control, BRS could not be calculated during the occlusion in these six patients.

Another major finding of the study was the significant coronary occlusion-induced weakening of the linear relationship between RR intervals and preceding systolic pressures after phenylephrine injections. Hence, the average correlation coefficient of the baroreflex regression decreased from 0.81 ± 0.27 to 0.47 ± 0.44 ($p < 0.0001$) during coronary artery occlusion in the 41 patients with systolic pressure rises after both phenylephrine tests (minimum 12 mm Hg during the occlusion). In 13 of these patients, there was no significant association between RR intervals and rising systolic pressures during coronary occlusions. In 11 of these patients, the rise in systolic pressure caused no change in heart rate, and in 2 cases, the decrease in heart rate was inconsistent and started before the phenylephrine bolus (Fig. 1). The correlation coefficient of the baroreflex regression was inadequate in three patients prior to coronary occlusion, and two of them developed hypotension during the coronary occlusion; the third patient had an inadequate correlation coefficient of the baroreflex slope also during coronary occlusion.

Coronary occlusion reduced BRS from 5.2 ± 3.8 to 4.1 ± 3.5 ms·mm Hg^{-1} ($p = 0.01$) in the 28 patients with preserved arterial baroreceptor control of heart rate—that is, adequate pressure response and correlation coefficient of the baroreflex slope also during the coronary occlusion. The mean estimated BRS during the coronary occlusion would have been 0.5 ms·mm Hg^{-1} in the 13 patients excluded owing to inadequate correlation coefficients (Fig. 1) and −3.5 ms·mm Hg^{-1} in the six patients excluded because of a paradoxical fall in systolic pressure (Fig. 2).

Determinants of arterial baroreflex control. In linear regression analysis, age was the only independent predictor of BRS both in baseline ($\beta = -0.23$, $p < 0.001$, $n = 44$) and during the coronary occlusion ($\beta = -0.39$, $p < 0.05$, $n = 28$). The BRS was not related to the phenylephrine-induced pressure rise either at baseline ($r = -0.08$) or during coronary occlusion ($r = 0.03$, $n = 28$), and the pressure rise in the 28 patients was only slightly lower during the coronary occlusion than in the baseline (28.5 ± 17.6 vs. 35.6 ± 11.9 mm Hg ($p = 0.05$). Loss of arterial baroreflex control of heart rate—that is, fall in systolic pressure with no tachycardia or loss of statistical association between RR intervals and preceding systolic pressures—occurred in 19 patients during coronary occlusion. This phenomenon occurred in all five patients who developed hypotensive reactions during the first coronary occlusion ($p < 0.01$) and was also predicted in univariate analysis by female gender ($p < 0.05$) and advanced age ($p < 0.05$) (Table 3). In stepwise logistic regression analysis, the only independent predictor of the loss of arterial baroreflex control was advanced age ($p < 0.05$). The site (anterior vs. inferior) of coronary occlusion did not predict BRS or any of the changes of baroreflex function (Table 3).

Control group. A control group of 11 patients was assessed to evaluate possible nonspecific changes in arterial baroreflex function that might occur during balloon inflation in a chronic total occlusion of a coronary artery. No significant changes in BRS (from 5.3 ± 4.0 to 5.2 ± 3.7 ms·mm Hg^{-1}), correlation coefficient of baroreflex slope (from 0.69 ± 0.34 to 0.73 ± 0.35) or phenylephrine-induced pressure rise (29 ± 12 to 30 ± 11 mm Hg) occurred.

Discussion

Our study documents impairment of human baroreflex control during acute myocardial ischemia caused by occlusion of a coronary artery. Baroreflex-mediated RR interval increases during phenylephrine-induced elevations of arterial pressure are attenuated, and the correlation between the RR interval and blood pressure changes during the pressure rise often weakens or becomes insignificant during the occlusion. Of interest, acute myocardial ischemia also reduces the

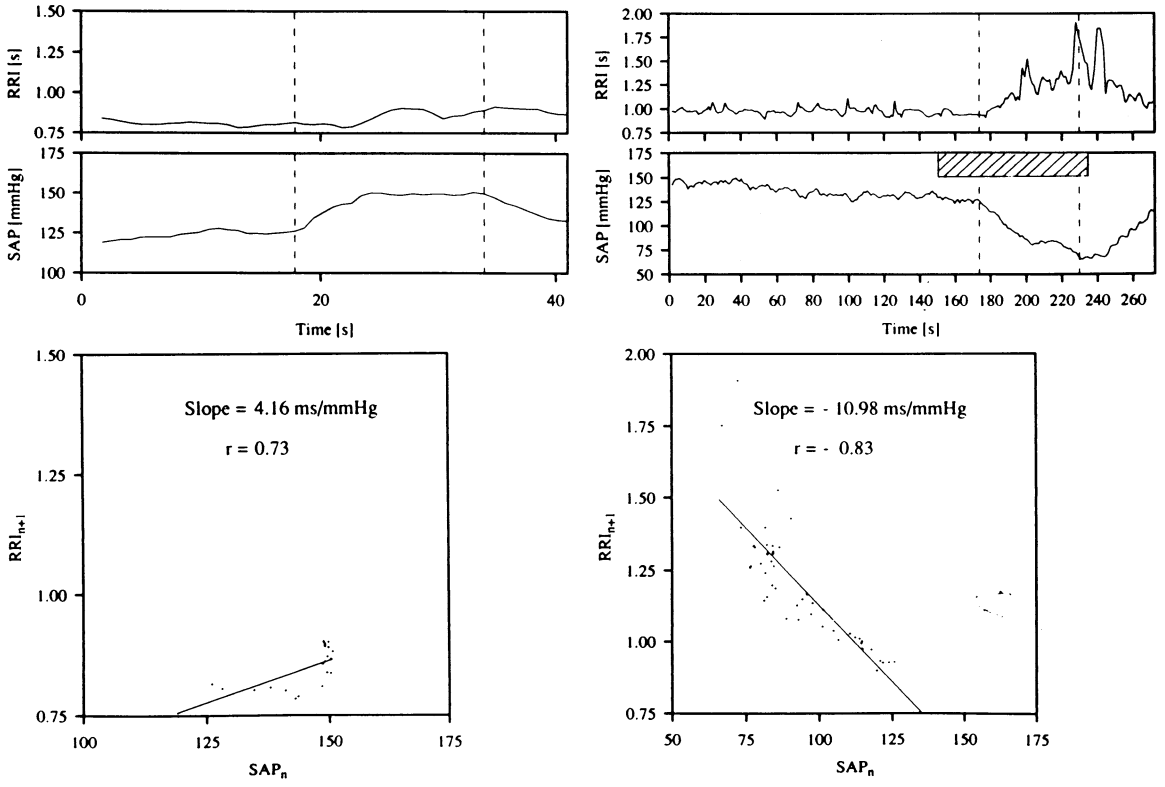


Figure 2. Computer output of beat-to-beat RR intervals and invasive systolic blood pressure (SAP) during phenylephrine tests in the baseline **(left upper panel)** and during balloon occlusion **(right upper panel)** of a 67% stenosis in left anterior descending coronary artery in a 62-year-old female patient. The lower panels show respective baroreflex slopes derived from the time windows shown by broken vertical lines in the upper panels. During coronary occlusion, the blood pressure falls despite the same phenylephrine dose (150 μg) as in the baseline test and the fall is accompanied by a paradoxical, progressive bradycardia. The resulting baroreflex slope would have been negative, but because of the loss of positive statistical correlation between the RR intervals and preceding systolic pressures these cases (n = 6) were excluded from the statistical analysis of correlation coefficients and baroreflex slopes. Coronary occlusion is shown by hatched bars **(right upper panel)**. Note the differences in the time scales and RR interval scales in the recordings.

phenylephrine-induced arterial pressure elevations during coronary occlusion.

Earlier studies. Our findings agree with those of earlier animal studies showing that coronary occlusion causes marked impairment of baroreflex control of the circulation (1–5). There is, however, limited information on the effect of coronary occlusion on human baroreflexes. Earlier clinical studies showed that baroreflex control of heart rate is attenuated during the early days of acute myocardial infarction (6–8). Pomidossi et al. (9) measured BRS in 20 patients by giving bolus injections of nitroglycerin during and after ~10-min episodes of asymptomatic and symptomatic myocardial ischemia and observed smaller RR interval shortenings during than after the ST segment depressions. Our study extends these earlier works in several ways and is the first to focus on the pathophysiology of arterial baroreflex during the initial phase of abrupt coronary occlusion, a critical period for out-of-hospital sudden death.

Background for impairment of baroreflex control of heart rate. Although we have no certain information regarding the mechanisms responsible for our findings, earlier animal research provides helpful clues. Occlusion of a coronary artery abruptly increases firing of nonmedullated vagal afferent fibers, excites efferent cardiac vagal neurons and inhibits efferent sympathetic activity (1,23–26). Acute myocardial ischemia can also excite cardiac sympathetic afferent nerves, and reciprocally inhibit efferent cardiac vagal nerve activity and increase efferent sympathetic activity (27,28). Inferential evidence from humans points more to stimulation of afferent vagal than sympathetic fibers during the early stages of abrupt coronary occlusion regardless of the site of the occlusion (11,12). Numerous experimental studies have shown that excitation of cardiac vagal afferent fibers exerts a profound inhibitory influence on the carotid baroreflex (1,2,25,29), and there is also evidence that sympathetic afferent activity interferes with vagal arterial baroreflex (30). Whatever mechanism is responsible, the most likely explanation for arterial baroreflex impairment during coronary occlusion is increased traffic carried over afferent cardiac nerves. This explanation does not exclude possible contributions from afferent cardiac nerve fibers secondary to distension of cardiac chambers due to increases of preload (31).

Other potential mechanisms that might contribute to the

Table 3. Clinical Characteristics and Signs of Ischemia in Patients With Preserved Arterial Baroreflex Function (Group 1) and Those With Impairment of Arterial Baroreflex of Heart Rate*

	Group 1 (n = 28)	Group 2 (n = 19)	p Value
Men	20 (71%)	7 (26%)	<0.05
Age (years)	54 ± 11	62 ± 9	<0.05
Occluded vessel			NS
Left anterior descending	18 (64%)	15 (79%)	
Left circumflex	7 (25%)	3 (16%)	
Right coronary	3 (11%)	1 (5%)	
ST changes	16 (57%)	15 (79%)	NS

Data presented are mean value ± SD or number (%) of patients. *Defined as inadequate pressure rise or correlation coefficient of the baroreflex regression, during balloon occlusion of a coronary artery stenosis.

attenuation of baroreflex function include ischemia-induced blood pressure changes. Blood pressure levels were slightly higher during coronary occlusion (Table 2), but saturation of the baroreflex due to a high blood pressure level is unlikely to be responsible for the attenuation. Systolic pressures were still in the range where human baroreflex slopes are reported to be linear (32), and the impairment we documented was unrelated to the blood pressure level. In accordance with earlier experience (33), this study showed no relation between BRS and degree of phenylephrine-induced pressure rise. Similarly, the changes of baroreflex function are unlikely to be a nonspecific phenomenon related to coronary angioplasty, because the intracoronary balloon inflation protocol without myocardial ischemia in the control group was not associated with changes of baroreflex function. Complex interactions between α-adrenergic stimulation and high efferent vagal activity at the pre- and postsynaptic levels of the sinus node may also contribute to the observed unstable behavior of heart rate in response to the phenylephrine-induced pressure rises during myocardial ischemia (34).

Blood pressure reactions during myocardial ischemia. During arterial hypotension, unloading of arterial and cardiopulmonary baroreceptors should increase sympathetic nerve activity and cause peripheral vasoconstriction. In contrast, when hypotension accompanies acute myocardial ischemia, increased stimulation of cardiac vagal afferents may inhibit the arterial baroreflex and even override the arterial baroreceptor reflex, resulting in peripheral vasodilatation and increased cardiac vagal efferent activity, despite a reduction in arterial blood pressure (1,2,24,25). The present study shows that such reflex hypotension also occurs in humans despite α-stimulation by phenylephrine, and that baroreflex slopes would become paradoxically negative in these cases because of the concomitant bradycardic reaction (Fig. 2). This type of reaction may occur both during anterior and inferior wall ischemia, contrary to the prevalent belief that vagal activation mainly occurs during inferior myocardial ischemia. Reduction in the responsiveness to α-adrenergic stimulation—that is, diminished phenylephrine-induced blood pressure rise—is in agreement with earlier animal experiments (1).

Methodological considerations. We quantitated baroreflex gain with the phenylephrine technique because this method is the "gold standard" (34) and has been used to obtain prognostic information on patients (35,36). Balloon occlusion of a coronary artery is a widely used model for controlled myocardial ischemia, but it fails to mimic natural circumstances in many respects. For ethical reasons, the occlusion time was limited here to a maximum of 2 min; therefore, our results describe only the initial changes of baroreflex function during the coronary occlusion.

Clinical significance of impaired baroreflex control. Abrupt occlusion of a coronary artery is a major cause of sudden cardiac death (13). Experimental studies have shown that augmented parasympathetic activity has protective and antifibrillatory effects during acute myocardial ischemia (14–16,37,38). Similarly, low BRS during myocardial ischemia is a predictor of vulnerability to fatal ventricular arrhythmia during experimental coronary occlusion and after myocardial infarction (14–16,35–38). The present study shows that the afferent signals from the ischemic myocardium have a greater significance than do those from the arterial baroreceptors in the modulation of vagal cardiac efferent activity and also peripheral vascular tone. This interference may be physiologically advantageous and limit cardiac sympathetic outflow induced by hypotension and baroreceptor withdrawal, but it may sometimes lead to severe hemodynamic instability. The clinical significance of impairment of arterial baroreflex regulation during acute coronary events merits further investigation.

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